Patent Office
Canberra

I, PETER GREGORY COLLIER, MANAGER AUSTRALIAN RECEIVING OFFICE, hereby certify that the annexed is a true copy of International Application No. PCT/AU97/00248 filed at the Australian receiving Office on 23 April 1997.

I further certify that this International Application claims priority from Provisional Application No. PN9407 lodged on 23 April 1996.

CERTIFIED COPY OF PRIORITY DOCUMENT

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

WITNESS my hand this
Fifteenth day of June 1999

PETER GREGORY COLLIER
MANAGER
AUSTRALIAN RECEIVING OFFICE

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/AU 97 / 00248
International Application No.

23 APR 1997 (23.4.97)
International Filing Date

AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* IRN 488342

Box No. I TITLE OF INVENTION

TASTE MASKED PARACETAMOL COMPOSITIONS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

F. H. FAULDING & CO. LIMITED
115 Sherriff Street,
Underdale, South Australia 5032
Australia

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: AU

State *(i.e. country)* of residence: AU

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

LUKAS, Stefan
38 Barrington Avenue,
Enfield, South Australia 5085
Australia

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AU

State *(i.e. country)* of residence: AU

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PHILLIPS ORMONDE & FITZPATRICK
367 Collins Street
Melbourne, Victoria 3000
Australia

Telephone No. (03) 9614 1944

Facsimile No. (03) 9614 1867

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

EVANS, Allan Mark
10 Gordon Terrace
Rosslyn Park, South Australia 5072
Australia

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: AU

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

DWYER, Mark
"Markarie"
Allendale North, Via Kapunda
South Australia 5373
Australia

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AU

State *(i.e. country)* of residence: AU

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

PITMAN, Ian Hamilton
Unit 4, 182 Gover Street
North Adelaide, South Australia 5006
Australia

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AU

State *(i.e. country)* of residence: AU

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] AP ARIPO Patent: KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] AL Albania
- [X] AM Armenia
- [X] AT Austria
- [X] AU Australia
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina
- [X] BB Barbados
- [X] BG Bulgaria
- [X] BR Brazil
- [X] BY Belarus
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China
- [X] CU Cuba
- [X] CZ Czech Republic
- [X] DE Germany
- [X] DK Denmark
- [X] EE Estonia
- [X] ES Spain
- [X] FI Finland
- [X] GB United Kingdom
- [X] GE Georgia
- [X] HU Hungary
- [X] IL Israel
- [X] IS Iceland
- [X] JP Japan
- [X] KE Kenya
- [X] KG Kyrgyzstan
- [X] KP Democratic People's Republic of Korea
- [X] KR Republic of Korea
- [X] KZ Kazakstan
- [X] LC Saint Lucia
- [X] LK Sri Lanka
- [X] LR Liberia
- [X] LS Lesotho
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova
- [X] MG Madagascar
- [X] MK The former Yugoslav Republic of Macedonia
- [X] MN Mongolia
- [X] MW Malawi
- [X] MX Mexico
- [X] NO Norway
- [X] NZ New Zealand
- [X] PL Poland
- [X] PT Portugal
- [X] RO Romania
- [X] RU Russian Federation
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia
- [X] SK Slovakia
- [X] TJ Tajikistan
- [X] TM Turkmenistan
- [X] TR Turkey
- [X] TT Trinidad and Tobago
- [X] UA Ukraine
- [X] UG Uganda
- [X] US United States of America
- [X] UZ Uzbekistan
- [X] VN Viet Nam

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- [X] YU Yugoslavia
- [X] GH Ghana
- [ ] .....
- [ ] .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) AU	23 April 1996 (23.4.96)	PN 9407	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 4	sheets	✓
2. description	: 30	sheets	✓
3. claims	: 3	sheets	✓
4. abstract	: 1	sheets	✓
5. drawings	: 4	sheets	✓
Total	: 42	sheets	✓

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

PHILLIPS ORMONDE & FITZPATRICK
Agents for Applilcant per:

.....

(Debbie Yin Foo PhD)

For receiving Office use only

1. Date of actual receipt of the purported international application: 23 APR 1997 (23.4.97)		2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority specified by the applicant: ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

TASTE MASKED PARACETAMOL COMPOSITIONS

The present invention relates to a paracetamol composition, in particular to a taste masked paracetamol composition capable of sustained release or immediate release having improved release characteristics and coating characteristics, and having less than 23% by weight ethyl cellulose. The present invention also includes a method of preparing such a composition preferably incorporating a spray drying technique.

Many pharmaceutical drugs have unpleasant tastes and therefore the oral administration of the pharmaceutical drug is often an unpleasant experience, particularly for those who find it difficult to swallow whole dosage forms. The pharmaceutical drug remains in the mouth for a time sufficient to impart its unpleasant taste sometimes resulting in the patient expelling the dosage form. Paracetamol, for example, can leave a strong and lasting bitter taste in the mouth.

Artificial flavourings and sweeteners have often been used to mask the taste by generally overwhelming the taste of the pharmaceutical. However, these are often unsuccessful and the bitter taste remains in the taste or remains as a lingering after taste if small particles of drug linger in the mouth.

Other methods of masking the taste include coating the drug with a polymeric material such as ethyl cellulose or a lipid based formulation such as paraffins, waxes, beeswax, higher fatty acids, higher fatty acid esters, glycerin fatty acid esters, and/or poly propylene glycols so as to create a barrier and delay the dissolution of the drug. However, these lipid based formulations are generally not effective at taste masking on their own and often require a polymer such as ethyl cellulose to complete the taste masking of the drug. Moreover, these methods of masking the taste make it difficult to tablet the pharmaceutical composition.

In US 4,767,789, ethyl cellulose has been used to coat acetaminophen to mask the bitter taste. However, the lower limit of ethyl cellulose is 24% by weight and it is explicitly stated that taste masking of acetaminophen is not achieved if the ethyl cellulose falls below this limit. Spray drying processes used to coat acetaminophen generally fail to provide taste masking at low ethyl

cellulose concentrations as it is considered that the coat is porous and irregular with roughened surfaces and this leads to ineffective taste masking due to rapid release of the pharmaceutical from the dosage form.

Such low coating compositions may also affect sustained release characteristics and often to gain such controlled release, dense polymer films of substantial thickness are necessary for sustained release. It is generally perceived that low coat composition would release the pharmaceutical too quickly. Porous membranes fail to provide sustained release and when coated by spray drying techniques the coating at low levels of coating polymer would tend to be rather porous, making them inadequate for taste masking and sustained release. (Deasey, P.B. (1984) In: Microencapsulation and Related Drug Processes, Chapter 8 pp 181-192, Marcel Dekker, Inc. N.Y.).

Analgesics are often administered over a time period so as to maintain a desirable and effective level of analgesia. Often, the administration is too frequent thereby necessitating a constant monitoring of the time periods.

At present, non-steroidal anti inflammatory drugs (NSAIDS) are used frequently to reduce pain, particularly in arthritis and rheumatism sufferers. However, NSAIDS can have undesirable side-effects. Paracetamol provides effective pain relief. Present dosages are immediate release often with unpleasant tastes associated with the immediate release and require administration at least 4 times a day. The dosage form may be large and swallowing of these dosage forms may be difficult thereby remaining in the mouth long enough to release the paracetamol. This constant administration is therefore unpleasant to the patient because of the taste and the mode of administration.

It would be desirable to provide a paracetamol composition having a low ethyl cellulose concentration which improves taste masking and bioavailability of the paracetamol and which is flexible in application and capable of sustained release properties to delay release of paracetamol in one dosage form and to provide immediate release in another form. The present applicants have surprisingly found that paracetamol can be taste masked whilst being capable of sustained release and/or immediate release with a single coating material,

such as ethyl cellulose as low as 23% and less. Preferably the paracetamol is coated by using a spray drying technique. Previously to obtain all three properties it was required to treat the pharmaceutical separately with the desired feature in mind. For instance, if taste masking and sustained release were to be incorporated in one dosage form, the pharmaceutical would be treated separately for either taste masking and then for sustained release.

Accordingly, it is the object of the present invention to overcome or at least alleviate one or more of the difficulties related to the prior art by providing a taste masked paracetamol composition capable of sustained release and/or immediate release in a single coated composition which uses less coating material. This improvement may provide flexibility in bioavailability of the paracetamol, reduce the cost in providing a taste masked formulation and improve the dosing regime.

Accordingly, in a first aspect of the invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said ethyl cellulose provides a substantially continuous coating on the core element.

The paracetamol composition has a coating of 23% ethyl cellulose. Such low coat weights of ethyl cellulose would generally be perceived as inadequate to provide sustained release.

By the term "capable of sustained release and/or immediate release" we mean that the compositon is flexible in its application and may be sustained release in one dosage form such as a powder but becomes immediate release in a tablet form whilst maintaining the taste masking properties.

In a preferred aspect of the present invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said ethyl cellulose provides a substantially continuous coating on the core element and when the composition is sustained release the rate of release of paracetamol is in the range of 10% to 44% in 45 mins.

Preferably the rate of release of paracetamol is in the range of 24% to 35% in 45 mins.

A sustained release profile allows for a slow release of the pharmaceutically active ingredient from a dosage form. The total daily dose recommended for paracetamol in adults is 4g/day. This is generally delivered as 4 divided dosages. The present invention allows for a reduced number of deliveries per day whilst maintaining a level of analgesic to attain pain relief. Preferably the dosage is in 2 divided dosages/day. Most preferably the dosage is one dosage/day. When the dosage is two dosages/day, the amount is preferably 2g/12hrs. When the dosage is one dosage/day, the amount is preferably 4g/24hrs. However, at such large dosages, the delivery of paracetamol is limiting. Large tablets cannot be swallowed.

This dosage regime is particularly achieved when the taste masked paracetamol of the present invention is in a powder form having sustained release properties. An advantage of a powdered form is that higher doses can be administered without the need to swallow large tablet forms. The powder may be administered in the absence of other excipients (required in tablets) and carriers. The powder may be mixed in a drink or sprinkled on food.

Preferably, the dosage results in a plasma concentration of paracetamol which does not fall below approximately 4mg/l and remains well below approximately 20mg/l. In a review by Prescott (Paracetamol, A Critical Bibliographic Review, Taylor & Francis, London, 1996, p.228-229) the therapeutic range for effective analgesia is about 5 to 20mg/l, with a similar range for anti-pyretic activity.

With conventional dosages (1g every 6 hours or 4g a day in 4 divided doses) the mean trough plasma concentration was 3mg/l and the mean

maximum concentration was about 12mg/l (Nielson *et al* . (1991) British Journal of Clinical Pharmacol. 31, 267-270).

Accordingly in a preferred aspect, the present invention provides a taste masked paracetamol composition as described above which may provide good antipyretic and analgesic control over 24 hours.

The core element in the coated pharmaceutical composition according to the present invention preferably may include up to 100% by weight of paracetamol.

The core element may be of any suitable size. Most preferably the core element has a particle size distribution with a median of about 100μm. The particles in the distribution may vary from about 1μm to about 250μm, more preferably from 25μm to 250μm. If the median of the distribution is close to either extreme of the distribution, the taste masking or sustained release characteristics may be affected. Preferably, in a range of 25μm to 250μm, no more than 25% of particles will be less than 25μm and no more than 2% will be over 250μm.

The major polymer in the coating material is a water insoluble polymer of ethyl cellulose.

The coating material is less than 23% of the total weight of the composition. This level of coating effectively provides taste masking characteristics and is capable of further providing sustained release and/or immediate release. However it is preferable that the coating material constitute less than 20% of the total composition and still provide taste masking with the capability of sustained release and/or immediate release.

The coating material according to the present invention may take any suitable form which provides a continuous coating and still provides taste masking and is capable of sustained release and/or immediate release.

The substantially continuous coat is substantially hole-free. The substantially continuous nature of the coating may be achieved by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the coating composition including a polymer in a solvent in a drying

gas having a low dew point. The dew point may preferably be less than 0°C, more preferably less than approximately -15°C.

By "substantially continuous coating" we mean a coating which retains a smooth and continuous appearance when magnified 1000 times under a scanning electron microscope and wherein no holes or breakage of the coating is evident so as to reduce taste masking.

Typical coatings may be in the range of approximately 0.005 to 25μm, preferably approximately 0.05μm to 5μm.

The solvent which may be used in the preparation of the coating of the composition may be an organic solvent. The solvent may be such that it constitutes a good solvent for the coating material but it is substantially a non-solvent or poor solvent for the pharmaceutically active ingredient. Whilst the active ingredient may partially dissolve in the solvent, in this aspect of the invention, the active ingredient will precipitate out of the solvent during the spray drying process much more rapidly than the coating material.

The solvent may be selected from alcohols such as methanol, ethanol, halogenated hydrocarbons such as dichloromethane (methylene chloride), hydrocarbons such as cyclohexane, and mixtures thereof. Dichloromethane (methylene chloride) has been found to be particularly suitable.

The concentration of polymer in the solvent will normally be less than 75% by weight. Normally the concentration will be in the range of 10-30% by weight.

Where the polymer is ethyl cellulose, the solvent is preferably methylene chloride. The concentration of ethyl cellulose is preferably in the range of 5-10% most preferably 7% by weight based on the total concentration of the coating material.

The paracetamol, provided in a form suitable for coating may be suspended in the coating material/organic solvent solution, preferably in an ethyl cellulose/methylene chloride solution at a concentration in the range of 10-30% by weight, preferably in the range of 14-20% by weight.

In a preferred aspect of the invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element; and

wherein said composition exhibits a reduced dissolution profile when the composition is sustained release.

The dissolution profile of the paracetamol composition may be reduced by approximately 25%, preferably approximately 40%, more preferably approximately 50%, relative to a standard form, preferably when measured at a pH approximately that of the mouth, for example a pH of approximately 6.8 in the period of 0 to approximately 45 minutes, preferably 0 to approximately 20 minutes.

By "dissolution profile" as used herein, we mean a plot of amount of active ingredient released as a function of time. The dissolution profile may be measured utilising the Drug Release Test (724) which incorporates standard test USPXXII 1990. (Test (711) Supplement VI, 1992). The dissolution tests may be conducted in a modified flow through cell apparatus. A profile is characterised by the test conditions selected. Thus the dissolution profile may be generated at a preselected temperature, flow rate and pH of the dissolution media.

Accordingly, the present invention further provides a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23 % by weight of the total weight of the composition, and

wherein the core element is selected for a size in the range of 0.1μm to 250μm and shape which facilitates coating and wherein said coating provides a continuous coating on the core element.

Applicants have found that the successful sustained release and/or immediate release and taste masking greatly depends on the completeness of the coating on the core element. This may be influenced by parameters such as the size and shape of the core element to be coated. Where the size and shape is favourable for coating, very low levels of coating material can be used to coat the core element such that sustained release and/or immediate release, taste masking and a continuous coating is achieved.

The particle size distribution of the core element dictates the surface area to be coated. If the core element is too small, very large surface areas need coating.

The size of the core element may be selected so that there will be no substantial breakage of the coat if the pharmaceutical composition is masticated so as to cause immediate release of the drug leaving a very distinctive unpleasant taste. The particles are preferably small enough to pass into curves and depressions in the mouth and between the teeth and avoid substantial breakage.

Preferably the core element has a particle size distribution of 1μm to 250μm with a median particle size of 100μm. More preferably the distribution is from 25μm to 250μm and most preferably from 35-125μm. As discussed above, the particle size distribution will include particles falling outside this range. These particles can also be coated to achieve the sustained release and taste masking properties.

In a further preferred aspect of the present invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23 % by weight of the total weight of the composition, and

wherein the core element is selected for a size in the range of 1μm to 250μm and shape having a low aspect ratio which facilitates coating and wherein said coating provides a continuous coating on the core element.

Shape can also influence the coverage and stability of the coat. Sharp angles on a crystal can cause weaknesses in the coat. These sharp corners may lead to stress points on the coat and cause weaknesses in the structure possibly leading to premature release of the pharmaceutical from the pharmaceutical composition.

Where the coat is thinner at the vertices this leads to more rapid release.

The composition according to the present invention is applicable to paracetamol which has a crystalline morphology and particularly a low aspect ratio. The aspect ratio is a measure of the length compared to the breadth. For example, an aspect ratio of 1 would be a box or sphere. The higher the aspect ratio, the more pointy and needle-like crystals will be.

The crystal geometry may result in a relatively thin coat at the crystal needle tips the release rates may be more rapid than is preferred with such actives. Similarly, where the pharmaceutically active ingredient exhibits high water or organic solvent solubility, the release rates may be more rapid than is required in a particular application. Furthermore, areas of thin coating are susceptible to breaking and cracking and hence ineffective for sustained release and taste masking.

Applicants have found that a spherical shape of the particle is most advantageous for both stability of the coat and high payload of active pharmaceutical. Therefore, it is most preferable that the aspect ratio is less than 3, more preferably 1-2, most preferably the aspect ratio is approximately 1 providing a substantially rounded shape. More preferably, the aspect ratio is 1 and the shape is round.

It is also preferable for most particles to be of the same size and shape. Inconsistencies in size and shape can lead to inconsistent coating. Where the drug particles are of different size and shape, polymeric coating materials such as ethyl cellulose will deposit differently on each particle. It is therefore preferable to have all particles the same size and shape so that the coating process is better controlled and maintained.

The present invention also provides a method of preparing a taste masked paracetamol composition capable of sustained release and/or immediate release including :

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element;

which process includes:

providing a sufficient amount of:

paracetamol selected for a size in the range of 1μm to 250μm and shape suitable for coating to provide a continuous coating;

a solution of a coating material including ethyl cellulose and an organic solvent being selective for ethyl cellulose;

suspending or dispersing the paracetamol in the solution;

spray drying the suspension or dispersion of paracetamol in a dry gas having a low dew point; and

collecting the paracetamol having a coating of ethyl cellulose of less than 23% by weight based on the weight of the total weight of the composition.

A slurry and paracetamol/ethyl cellulose/methylene chloride may be atomized preferably using a 2 fluid nozzle into a spray dryer to form coated powder.

For paracetamol, it is preferable that the particles are in the range of 1 to 250μm, preferably in the range of 35 to 125μm and are spherical in shape having a low aspect ratio.

Spray drying of the paracetamol and ethyl cellulose in the solvent involves spraying a stream of air into an atomised suspension so that solvent is caused to evaporate leaving the paracetamol coated with the ethyl cellulose.

Preferably, for a solvent such as methylene chloride, the solvent concentration in the drying chamber is maintained above 40,000 parts, more preferably in the range of approximately 40,000 to 100,000 parts per million of organic solvent.

The spray-drying process for such solvents may be conducted at a process temperature of from approximately 5°C to 35°C.

The utilisation of a drying gas exhibiting a low dew point aids the production of a substantially continuous coating. It has also been found that the presence of a solvent during the drying step slows the evaporation rate of the solvent such that a substantially continuous coat exhibiting reduced permeability is produced. These two factors may be interrelated. Thus the higher the drying gas dew point, the higher the solvent vapour pressure required in the system to give a substantially continuous coat.

The drying process may be of any suitable type.

Spray drying of the pharmaceutical compositions may be undertaken utilising either rotary, pneumatic or pressure atomisers located in either a co-current, counter-current or mixed-flow spray dryer or variations thereof.

The drying gas may be heated or cooled to control the rate of drying. A temperature below the boiling point of the solvent may be used. Inlet temperatures will typically be in the range of from approximately 40°C to 120°C and outlet temperatures approximately 5°C to 35°C.

The present invention permits the optimisation of the coat formation to meet the needs of the material or application. Adjusting the coating composition allows modification of the release profile for the material. Controlling the process parameters including temperature, solvent concentration, spray dryer capacity, atomising air pressure, droplet size, viscosity, total air pressure in the system and solvent system, allows the formation of a range of coats, ranging from dense, continuous, non-porous coats through to more porous particle/polymer matrices.

The spray drying process may utilise a method employing a nozzle to atomise the paracetamol in ethyl cellulose/methyl cellulose solution. Preferably pneumatic atomisation is used. The nozzle produces individual droplets suspended in a polymeric coating material/organic solvent solution. Removal of the organic solvent results in a drug dosage unit coated with the polymeric coating material.

Preferably the nozzle is a 2 fluid nozzle. The ratio of solvent/drug to air is important in a 2 fluid nozzle and this may be varied by optimizing the relative positions of the outlet and inner passages. The operating conditions include variations on air inlet temperatures, air outlet temperatures, air pressures, feed rates of solvent and drug suspensions, atomisation, air quality and outlet diameters of inlet and outlet passages of the atomizer. Preferably, the air inlet temperature is approx 70-150°C, the air outlet temperature is in the range of 20-50°C, the air flow rate is in the range of 40-1300kg/hr, the feed rates of solvent and drug is in the range of 3-100 kg/hr, atomisation air quantity is in the range of 6-100 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 1-10 mm and 2-15 mm in diameter respectively.

More preferably, the air inlet temperature is approx 100°C, the air outlet temperature is in the range of 25-35°C, the air flow rate is in the range of 40-80kg/hr, the feed rates of solvent and drug is in the range of 8-9 kg/hr, atomisation air quantity is in the range of 7-9 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 2-3 mm and 4-6 mm in diameter respectively.

The product may be collected by any means available to the skilled addressee. Preferably the collection method is by sock filters or cyclone collection.

The final product will have an ethyl cellulose coating of less than 23% by weight and still maintain taste masking and be capable of sustained release and/or immediate release in a single composition. Preferably the final product is paracetamol having 79-84% by weight paracetamol and 16-21% by weight ethyl cellulose.

Most preferably, the paracetamol is a taste masked composition of 80% by weight paracetamol and 20% by weight ethyl cellulose. The average size of the paracetamol final product is approximately 125μm.

The present invention further provides in a preferred aspect, a post-treatment step to remove residual solvent. The post treatment may include a post drying step including drying the final product on a tray and drying the product at a bed temperature sufficient to remove excess solvent but not

degrade the pharmaceutical drug. Preferably the temperature is in the range of 35°C to 45°C, most preferably at 40°C.

The pharmaceutical composition may be in the form of a powder of particle size in the range of 1μm to 250μm, preferably in the range of 35μm to 125μm. Most preferably the particle size distribution has a median of 100 μm. The small particle size ensures that the particles have a substantially non-gritty feel in the mouth. The small particle size may also minimise break-up of the particles cin the mouth, for example by the teeth. When in the form of a powder the composition is sustained release and may be administered directly into the mouth or mixed with a carrier such as water, or semi-liquid compositions such as syrups, yoghurt. Preferably, the pharmaceutical composition is a powder which is mixed with water prior to ingestion.

The taste masked paracetamol may be further provided in any suitable unit dosage form. The pharmaceutical composition may be provided in a form selected from sprinkles, sachets, chewing gums, tablets; including chewable tablets, gums, lozenges, liquids, suspensions, filled capsules; including filled gelatine capsules. The flexibility of release is provided by the form in which the paracetamol is delivered.

The coated paracetamol composition is primarily prepared as a powder which exhibits sustained release properties. The powder, when tabletted, shows immediate release properties but retains taste masking properties. The tablet form retains sufficient taste masking for a period long enough to avoid any taste whilst providing a dissolution profile fast enough to categorise the tablet as immediate release.

The process of tabletting may be conducted by any means available to the skilled addressee. Preferably, the tablet is formed by direct compression. More preferably, there are no granulation steps. The hardness of the tablets may be in the range of 3-15 kP, more preferably in the range of 5-9 kP.

The shape of the tablet is preferably round as this shape is most desirable for even compression.

Because of the sustained release characteristics of the paracetamol composition, it can be used as a means to treat pain-related disorders in which pain is experienced continuously over a period of time. Examples of such disorders include arthritis, rheumatism, muscle pains, morning stiffness and general pain relief.

Accordingly, there is provided a method of preventing and treating a pain-related disorder including administering an effective amount of a taste masked paracetamol composition capable of sustained release and/or immediate release including

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element.

In a preferred aspect of the invention there is provided a method of preventing and treating a pain-related disorder including administering an effective amount of a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element and when the composition is sustained release the rate of release of paracetamol is in the range of 10% to 44% in 45 mins.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention as specified above.

In the figures:

Figure 1 shows the mean subject plasma profiles for 6 healthy males after ingestion of 2 x 500mg Tylenol Extra strength Tablet (fasted)(--Δ--); 1 x 1000 mg Nopap Power (fasted)(--•--); or 1 x 1000 mg Nopap Powder (fed) (--[]--).

Figure 2 shows Predicted Steady-State Plasma Concentrations of Paracetamol (2g Dose of Nopap Powder every 12 hours). Data derived using mean plasma concentration versus time data for single dose administration of Nopap powder (Fasted) in Study SAL-1/96.

Figure 3 shows Predicted Steady-State Plasma Concentrations of Paracetamol (2g Dose of Nopap Powder every 12 hours). Data derived using mean plasma concentration versus time data for single dose administration of Nopap powder (Fed) in Study SAL-1/96.

Figure 4 shows mean plasma paracetamol concentration in a plasma bioavailability study after ingestion of 500 mg Nopap (fasted) (--□--); 500 mg Nopap (fasted) (--•--); or 500 mg Tylenol®(fasted)(--Δ--).

Example 1

Paracetamol Formulation - Nopap Powder

Ethyl cellulose is dissolved in methylene chloride and then paracetamol is dispersed in the solution, in the following formulation, to produce a slurry.

Ethyl cellulose N10 NF	7% w/w
Paracetamol	28% w/w
Methylene Chloride	65% w/w

This slurry is then spray dried under the following process conditions in a NIRO "PM" type 2 fluid atomiser.

Fluid Insert	1.3mm
Air Cap	5mm
Feed Rate	3 kg/hr or slurry
Atomising gas flow rate	5.6m^3/hr
Process gas Inlet Temperature	40°C
Process gas flow rate	20 m^3/hr

The final formulated product is a white, free flowing taste masked powder consisting of 80% paracetamol and 20% ethyl cellulose with a median particle size of less than 150μm.

Example 2

Pharmacokinetic Parameters from a single 1000mg dose of Tylenol Extra Strength Tablet vs Test Coated Paracetamol Powder (Nopap Powder)

A pilot study of 6 healthy males was conducted to evaluate pharmacokinetic parameters following injestion of 1000mg of a single dose of Tylenol Extra Strength Tablet (immediate release) and Test Coated Paracetamol Powder (Nopap) (sustained release, prepared according to Example 1).

METHODS

1000 mg of Tylenol® Extra Strength Tablet or Test Coated Paracetamol (Nopap) prepared according to Example 1 were administered to 6 healthy males. Plasma paracetamol concentrations were measured under fasted and fed conditions.

Tables 1, 2 and 3 summarise statistical comparisons. The arithmetic mean and individual pharmacokinetic parameters for each study treatment are shown in Table 4. Individual and mean subject plasma profiles are provided in Figure 1.

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment B versus Treatment A
(n=6)

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.739	17.244	-72.52	0.0001*	35.69	6.7 - 48.3	.	.	.
TMAX	2.917	0.582	401.43	0.0177*	3.15	231.1 - 771.7	.	.	.
AUC	39.377	46.930	-16.09	0.0227*	86.61	72.4 - 95.4	.	.	.
AUC_INF	41.863	48.137	-13.03	0.0222*	96.19	77.7 - 96.2	.	.	.
KEL	0.139	0.224	-37.92	0.0025*	49.30	44.6 - 79.6	.	.	.
THALF	5.232	3.153	65.91	0.0026*	17.28	135.2 - 196.6	.	.	.
LCMAX	1.519	2.815	-46.05	0.0001*	12.31	18.7 - 40.0	27.4	32.83	.
LAUC	3.654	3.835	-4.72	0.0227*	77.81	73.4 - 94.9	83.5	11.13	.
LAUC_INF	3.714	3.860	-3.80	0.0188*	93.59	78.1 - 95.4	86.4	8.65	.

Treatment B: 1x1000mg Hopap Powder, fasted (Batch No. 50089214) - Faulding - test
Treatment A: 2x500mg Tylenol Extra Strength tablet (Batch No. SEA704) - McNeil - reference, fasted.

Values for Treatments B and A are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Table 1

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment C versus Treatment B
(n=6)

Parameter	Treatment Means C	B	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.050	4.739	-14.55	0.7103	5.68	9.7 - 161.2	.	.	.
TMAX	6.000	2.917	105.71	0.0044*	7.84	151.8 - 259.6	.	.	.
AUC	38.805	39.377	-1.45	0.8367	72.62	84.9 - 112.2	.	.	.
AUC_INF	42.388	41.863	1.25	0.8188	91.00	90.6 - 111.9	.	.	.
KEL	0.140	0.139	0.37	0.9796	20.08	72.2 - 128.6	.	.	.
THALF	5.348	5.232	2.23	0.8155	44.50	83.7 - 120.8	.	.	.
LCMAX	1.354	1.519	-10.83	0.4109	12.31	58.0 - 124.0	84.8	32.83	.
LAUC	3.633	3.654	-0.58	0.7497	77.81	86.1 - 111.4	97.9	11.13	.
LAUC_INF	3.725	3.714	0.30	0.8315	93.59	91.5 - 111.8	101.1	8.65	.

Treatment C: 1x1000mg Nopap Powder, fed (Batch No. 50089214) - Faulding - test
Treatment B: 1x1000mg Nopap Powder, fasted (Batch No. 50089214) - Faulding - reference

Values for Treatments C and B are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (C - B) expressed as a percentage of Treatment B

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Table 2

Paracetamol Bioavailability Study No. SAL-1/96

Bioequivalence with respect to Plasma Paracetamol
Treatment C versus Treatment A
(n=6)

Parameter	Treatment Means C	A	Pct Difference	PR>|T|	Power (%)	90% Confidence Intervals	Mean Ratio	Intra Subject CV%	Inter Subject CV%
CMAX	4.050	17.244	-76.51	0.0001*	35.69	2.7 - 44.3	.	.	.
TMAX	6.000	0.582	931.52	0.0001*	3.15	761.2 -1301.8	.	.	.
AUC	38.805	46.930	-17.31	0.0164*	86.61	71.2 - 94.1	.	.	.
AUC_INF	42.388	48.137	-11.94	0.0320*	96.19	78.8 - 97.3	.	.	.
KEL	0.140	0.224	-37.69	0.0026*	49.30	44.8 - 79.8	.	.	.
THALF	5.348	3.153	69.61	0.0019*	17.28	138.9 - 200.3	.	.	.
LCMAX	1.354	2.815	-51.89	0.0001*	12.31	15.9 - 33.9	23.2	32.83	.
LAUC	3.633	3.835	-5.27	0.0137*	77.81	71.8 - 92.9	81.7	11.13	.
LAUC_INF	3.725	3.860	-3.52	0.0264*	93.59	79.0 - 96.5	87.3	8.65	.

Treatment C: 1x1000mg Nopap Powder, fed (Batch No. 50089214) - Faulding - test
Treatment A: 2x500mg Tylenol Extra Strength tablet (Batch No. SEA704) - McNeil - reference, fasted

Values for Treatments C and A are the least squares means (LSMEANS) from the ANOVA
Parameters with the L prefix are log-transformed

Pct Difference = difference between treatments (C - A) expressed as a percentage of Treatment A

. = value not calculated

PR>|T| = ANOVA test for significant differences between treatments

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test-reference) for log transformed parameters only

Table 3

Table 4

Study Design: Single dose (1000 mg) in 6 healthy volunteers with blood sampling over 24 hours.

TREATMENT A : Tylenol (fasted)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	14.032	0.67	51.18	51.88
2	17.996	0.33	53.94	55.62
3	10.011	1.5	34.29	34.96
4	19.322	0.33	49.27	50.93
5	20.513	0.33	39.9	40.97
6	21.592	0.33	53	54.46
MEAN	17.244	0.58	46.93	48.14

TREATMENT B : Nopap Powder (fasted)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	5.235	4	45.71	48.04
2	4.081	3	42.81	46.75
3	7.332	1.5	30.41	31.82
4	4.815	3.5	49.75	53.46
5	3.122	2.5	29.76	31.1
6	3.85	3	37.82	40.01
MEAN	4.739	2.92	39.38	41.86

TREATMENT C : Nopap Powder (fed)

Subject	CMAX(mg/L)	TMAX(hours)	AUC (mg.h/L)	AUC-INF(mg.h/L)
1	3.127	11	35.79	43.46
2	3.637	6	45.06	48.88
3	2.824	5	30.51	33.64
4	6.846	4	53.27	55.14
5	4.239	5	27.5	29.44
6	3.626	5	40.7	43.77
MEAN	4.050	6.00	38.81	42.39

DISCUSSION OF RESULTS

In evaluating formulations to determine bioequivalence, the 90% confidence intervals and mean ratios of the ln-transformed pharmacokinetic parameters CMAX, AUC and AUC-INF are compared.

(a) Comparison of Reference Tylenol Extra Strength Tablet (Fasted) vs Test Nopap Powder (Fasted) - refer Table 1

The 90% confidence interval and mean ratio for CMAX fell outside the allowed bioequivalence range of 80-125% and the difference was statistically significant, as would be expected for a sustained-release formulation compared with an immediate-release formulation. In fact, the mean CMAX value showed approximately a 70% reduction. Although the 90% confidence intervals for ln-transformed AUC and AUC-INF fell outside the lower limit allowed for bioequivalence and the difference was statistically significant for both parameters, the mean ratio values, which are a measure of bioavailability, were within the 80-125% "bioequivalence" range for both "extent of absorption" parameters (83.5% and 86.4% for AUC and AUC-INF, respectively). The mean TMAX values were 2.92 hours for Nopap powder and 0.58 hours for Tylenol Tablet and the difference was statistically significant, as would be expected of a sustained-release formulation compared with an immediate-release formulation.

Thus, under fasted conditions, Nopap powder exhibits sustained-release characteristics compared with Tylenol tablets with a significantly reduced rate of paracetamol absorption as evidenced by a significant reduction in CMAX and significant cincrease in TMAX. Only one subject, showed a reduced CMAX with Nopap powder (fasted) compared with Tylenol Extra Strength tablet (fasted), without an increase in TMAX (1.50 hours for both formulations).

(b) Comparison of Test Nopap Powder (Fasted) vs (Fed) - refer Table 2

The 90% confidence interval for CMAX fell outside the allowed bioequivalence range of 80-125%, however, the mean ratio value (84.8%) was included in the allowed bioequivalence range. In addition, food did not cause a significant reduction in CMAX ($p>0.05$). The 90% confidence intervals for ln-transformed AUC and AUC-INF fell within the range allowed for bioequivalence, the differences were not statistically significant, and the mean ratio values, which

are a measure of bioavailability, were within the 80-125% "bioequivalence" range for both "extent of absorption" parameters (97.9% and 101.1% for AUC and AUC-INF, respectively). The mean TMAX values of 6.00 hours for Nopap powder (fed) and 2.92 hours for Nopap powder (fasted) were statistically significantly different.

In accordance with FDA 1992 Bioequivalence Guidelines, for a sustained-release product to demonstrate a comparable food effect, the mean ratios of the ln-transformed least squares mean pharmacokinetic parameters AUC, AUC-INF and CMAX must fall within the 80-125% range. Therefore, based on these guidelines, Nopap powder is bioequivalent when administered under fasted and fed conditions, with the only effect of food being a significant lengthening of TMAX.

Table 3, summarises the comparison of Tylenol Extra Strength Tablet (Fasted) vs Tested Nopap Powder (Fed).

Example 3

Paracetamol Powder - Steady State Simulations

A single dose study based on results of Example 2 were used to predict 24 hour plasma concentration. Plasma concentration versus time profiles for twice daily administration of coated paracetamol powder (according to Example 1) were analysed.

In simulated studies coated paracetamol powder was administered as a dose of 2g every 12 hours. Hence, the total daily dose (4g) is in keeping with current dose recommendations for paracetamol in adults.

The results in Figure 2 show the plasma concentration-time profile using the single dose fasting data. Figure 3 shows the corresponding profile using the single dose fed data. Plasma levels would fall between these two extremes.

When dosed at a level of 2g twice a day, the plasma concentrations of paracetamol do not fall below 4mg/L and remain well below 20mg/L. As noted in a review by Prescott [Paracetamol, A Critical Bibliographic review, Taylor &

Francis, London, 1996, page 228-229] the therapeutic range for effective analgesia is about 5 to 20mg/L, with a similar range for antipyretic activity.

Furthermore, during repeated administration of conventional paracetamol at a dose of 1g every 6 hours (4g a day in 4 divided doses) the mean trough plasma concentration (immediately pre-dose) was 3 mg/L, and the mean maximum concentration was about 12 mg/L [Nielson *et al.* (1991) British Journal of Clinical Pharmacology 31: 267-270]. Accordingly in the coated paracetamol the predicted steady-state levels for coated paracetamol powder are within this range (see Figures 2 and 3).

In conclusion, the preliminary results suggest that the plasma concentrations of paracetamol obtained during twice daily administration of coated paracetamol powder will be within the range of concentrations encountered with four times daily dosing with conventional paracetamol formulations. One can speculate therefore that twice daily dosing with coated paracetamol powder according to the present invention would provide good antipyretic and analgesic control over 24 hours. Perhaps the most important advantage would be overnight pain relief, particularly for patients with arthritic conditions leading to morning stiffness.

Example 4

Paracetamol Formulation - Paracetamol Tablet

Tablets of paracetamol were prepared using the NoPap powder of Example 1. The powder was subjected to direct compression. No granulation steps were used before compression. The hardness of the tablets was in the range of 5 to 9 kP.

500 mg tablets were prepared having the following formulation:

Ingredient	Weight (mg)
NoPap powder (80% potent)	625
Mannitol	504.9
Flavours	59.1
Crospovidone	37.0
Magnesium Stearate	14.0
	1240.0

Example 5

Dissolution of Coated Paracetamol Nopap Powder and Nopap Tablets

Time (mins)	Powder	Tablet
2	1.80	12.81
5	4.32	38.48
10	8.07	73.97
20	15.11	
30		100.00
45	30.27	100.00

The dissolution profile is a plot of amount of active ingredient released as a function of time. The dissolution profile was measured utilising the Drug Release Test (724) which incorporates standard test USPXXII 1990. (Test (711) Supplement VI, 1992). The dissolution tests were conducted in a modified flow through cell apparatus.

Example 6

Paracetamol Bioavailability Study

Fourteen healthy male subjects were administered Test Formulation outlined below to study the bio availability of NoPap tablets compared immediate release Tylenol® Extra Strength tablets.

Study Formulations

Test Formulations:

NoPap C1: a taste-masked soft-chew tablet of paracetamol (500 mg)

NoPap C2: a taste-masked soft-chew tablet of paracetamol (500 mg)

Reference Formulation:

Tylenol® Extra Strength Tablet containing paracetamol (500 mg)

Treatments

Treatment 1: NoPap C1; 500 mg paracetamol as a single taste-masked soft-chew paracetamol tablet was administered with 240 mL of room temperature water following at least a 10 hour overnight fast.

Treatment 2: NoPap C2; 500 mg paracetamol as a single taste-masked soft-chew paracetamol tablet was administered with 240 mL of room temperature water following at least a 10 hour overnight fast.

Treatment 3: Tylenol® Extra Strength Tablet; 500 mg paracetamol as a single paracetamol tablet was swallowed whole with 240 mL of room temperature water following at least a 10 hour overnight fast.

For treatments 1 and 2, the tablet was chewed gently for a period of 30 seconds before swallowing. The mouth was then rinsed three times with aliquots of the 240 mL of the water used for dosing. All rinsing water was swallowed.

Sample Analysis

Study plasma samples were analysed for paracetamol concentration using a sensitive and specific high performance liquid chromatographic (HPLC) procedure involving ultraviolet detection. Samples were not identified to the analysts by treatment group, and all samples for a given subject (pre- and post-dose) were initially analysed together (along with standards and controls) in the same analytical run. The assay had a limit of quantitation of 0.16 mg/L and was linear over the range 0.16 mg/L to 16.00 mg/L.

Results

The results obtained by comparing the three treatments in the 14 evaluable subjects are shown in Figure 4. Table 5 shows the mean (standard deviation) values of the calculated pharmacokinetic parameters and observations for the three treatments.

PARACETAMOL BIOAVAILABILITY STUDY

TABLE 5

MEAN (±SD) PHARMACOKINETIC PARAMETERS AND OBSERVATIONS

N=14

PARAMETER	TREATMENTS		
	1	2	3
	NOPAP C1 FASTING	NOPAP C2 FASTING	TYLENOL® FASTING
AUCO-inf (mg.h/L)	22.782 (3.891)	21.806 (3.819)	21.389 (3.612)
AUCo-t (mg.h/L)	20.733 (3.336)	19.976 (3.299)	19.350 (2.849)
Relative Bioavailability (F%)	106.85 (7.63)	102.59 (13.03)	100
Cmax (mg/L)	6.330 (1.571)	7.297 (1.627)	7.332 (2.269
tmax (h)	0.558 (0.174)	0.576 (0.315)	0.800 (0.765)
t1/2 (h)	2.904 (0.407)	2.841 (0.453)	3.068 (0.707)
Ke (h-1)	0.2430 (0.0341)	0.2499 (0.0404)	0.2366 (0.0509)

Treatment 1: Nopap C1 paracetamol taste-masked soft-chew tablet (1 x 500 mg), administered following a 10 hour overnight fast.

Treatment 2: Nopap C2 paracetamol taste-masked soft-chew tablet (1 x 500 mg), administered following a 10 hour overnight fast.

Treatment 3: Tylenol® Extra Strength paracetamol tablet (1 x 500 mg), administered following a 10 hour overnight fast.

Discussion/Conclusions

1. The mean extent of paracetamol absorption (both AUC_{0-t} and AUC_{0-inf}) showed no significant difference between the three treatments, Nopap C1 (fasting), Nopap C2 (fasting) and Tylenol® Extra Strength tablets, based on confidence intervals using log-transformed data. All comparisons had confidence intervals within the acceptance 80-125% range.
2. The mean time to peak for both NoPap formulations, when given in the fasting state, were slightly less than Tylenol® Extra Strength Tablets, with NoPap C1 peaking earlier than NoPap C2, although the differences were not statistically significant.
3. Although the mean relative bioavailability of NoPap C1 was slightly higher than NoPap C2, the difference was not statistically significant.

The study data demonstrate that, under fasting conditions, single 500 mg doses of the test taste-masked, soft-chew paracetamol tablet, NoPap C2, exhibits similar rate and extent of absorption of paracetamol to that of the reference marketed formulation, Tylenol® Extra Strength tablets, which suggests that the taste masking process has not altered the release characteristics of the test drug.

Example 7

Evaluation of taste in Nopap Tablets

1. **Introduction**

This randomised 3-way cross-over study was conducted to evaluate the taste of three taste-masked paracetamol tablet (Nopap tablets) formulations in healthy adults. The tablets were prepared according to Example 1.

Each subject tasted the three formulations (Tablet A (Citrus), Tablet B (Mint), Tablet C (Berry). Immediately after tasting each tablet, the subject indicated his or her overall opinion of the taste (bitterness).

2. **Results**

2.1 Taste characteristics

Bitterness results are summarised in Table 6. Of the 77, 78 or 77 individuals tasting tablets A, B & C, 39%, 34.6% and 42.9% tasted no bitter taste in the Nopap tablets despite the immediate release characteristic of the tablet. Only 5.2%, 5.1% or 5.2% recorded any major bitterness in the tablet.

Finally it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.

Claims

1. A taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element.

2. A taste masked paracetamol composition according to claim 1 wherein the sustained release of the paracetamol has a rate of release in the range 10% to 44% in 45 mins.

3. A taste masked paracetamol composition according to claim 1 or 2 having a dosage of paracetamol such that upon administration a plasma concentration of the paracetamol is maintained in a range of approximately 4mg/l to approximately 20mg/l over a period of 24 hours.

4. A taste masked paracetamol composition according to claim 3 wherein the administration is at least one dosage/24 hours.

5. A taste masked paracetamol composition according to claim 3 or 4 wherein the administration is at least 2 dosages/24 hours.

6. A taste masked paracetamol composition according to any one of claims 1 to 5 wherein the core element has a particle size distribution in the range of 0.1μm to 250μm and a shape which facilitates coating to provide a continuous coating on the core element.

7. A taste masked paracetamol composition according to claim 6 wherein the particle size distribution is in the range of 35μm to 125μm.

8. A taste masked paracetamol composition according to claim 6 or 7 wherein the core element has a low aspect ratio.

9. A taste masked paracetamol composition according to claim 8 wherein the aspect ratio is approximately 1.

10. A taste masked paracetamol composition according to any one of claims 6 to 9 wherein the core element is substantially spherical.

11. A taste masked paracetamol composition according to any one of claims 1 to 10 wherein the coating material includes ethyl cellulose.

12. A taste masked paracetamol composition according to any one of claims 1 to 11 wherein the coating material provides a coat on the core element in the range of 0.005 to 25μm.

13. A taste masked paracetamol composition according to any one of claims 1 to 12 which is a powder having sustained release properties.

14. A taste masked paracetamol composition according to any one of claims 1 to 12 which is a tablet having immediate release properties.

15. A method of preparing a taste masked paracetamol composition capable of sustained release and/or immediate release including :

a core element including a paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said coating material provides a substantially continuous coating on the core element;

which method includes:

providing a sufficient amount of:

paracetamol selected for a size in the range of 0.1μm to 250μm and shape suitable for coating to provide a continuous coating;

a solution of a coating material including ethyl cellulose and an organic solvent being selective for ethyl polymer;

suspending or dispersing the paracetamol in the solution of coating material;

spray drying the suspension or dispersion of paracetamol in a dry gas having a low dew point; and

collecting the paracetamol having a coating of ethyl cellulose of less than 23% by weight based on the weight of the total weight of the composition.

16. A taste masked paracetamol composition prepared by the method according to claim 15.

17. A taste masked paracetamol composition according to claim 16 which is a powder of particle size in the range of 1μm to 250μm having sustained release properties.

18. A taste masked paracetamol composition according to claim 16 which is a tablet of compressed paracetamol powder having immediate release properties.

19. A method of preventing and treating a pain-related disorder including administering an effective amount of a paracetamol composition according to any one of claims 1 to 12, or 16 to 18.

20. A method according to claim 19 wherein the paracetamol composition is a powder having sustained release properties.

21. A sustained release and taste masked pharmaceutical composition according to claim 1 substantially as hereinbefore described with reference to the examples.

ABSTRACT

The present invention relates to a paracetamol composition, in particular to a taste masked paracetamol composition capable of sustained release or immediate release having improved release characteristics and coating characteristics, and having less than 23% by weight ethyl cellulose. The present invention also includes a method of preparing such a composition preferably incorporating a spray drying technique.

Accordingly, in a first aspect of the invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23% by weight of the total weight of the composition wherein said ethyl cellulose provides a substantially continuous coating on the core element.

In a further preferred aspect of the present invention there is provided a taste masked paracetamol composition capable of sustained release and/or immediate release including:

a core element including paracetamol; and

a coating material including ethyl cellulose of less than 23 % by weight of the total weight of the composition, and

wherein the core element is selected for a size in the range of 1μm to 250μm and shape having a low aspect ratio which facilitates coating and wherein said coating provides a continuous coating on the core element.

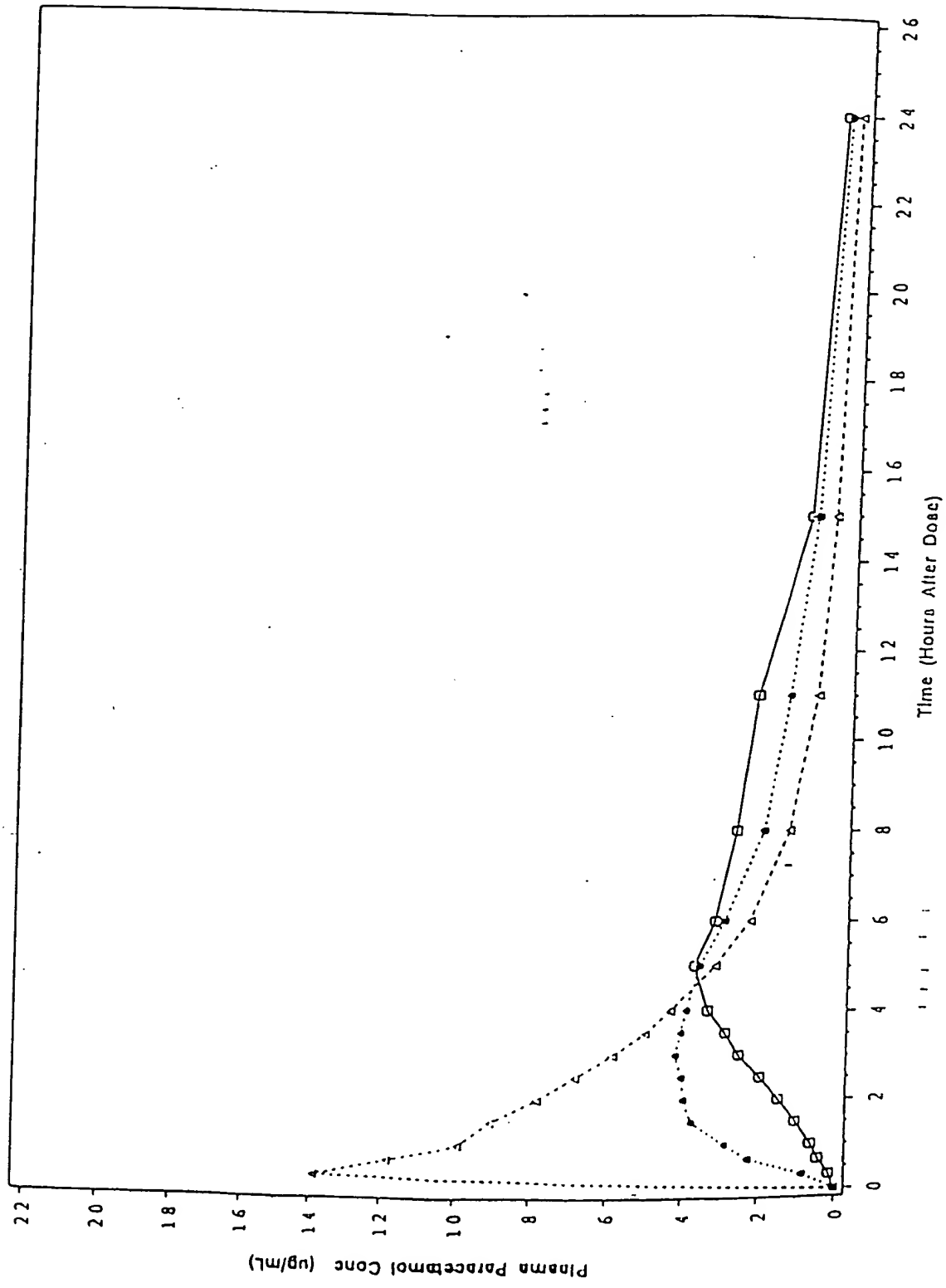
Plasma Paracetamol Conc (ug/mL)
0
2
4
6
8
10
12
14
16
18
20
22
Time (Hours After Dose)
0
2
4
6
8
10
12
14
16
18
20
22
24
26

Figure 1

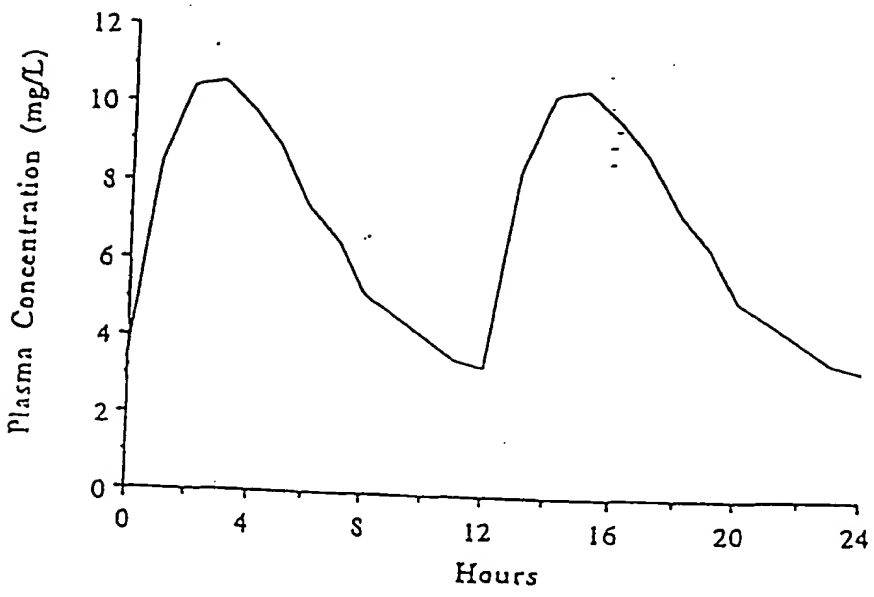

Figure 2

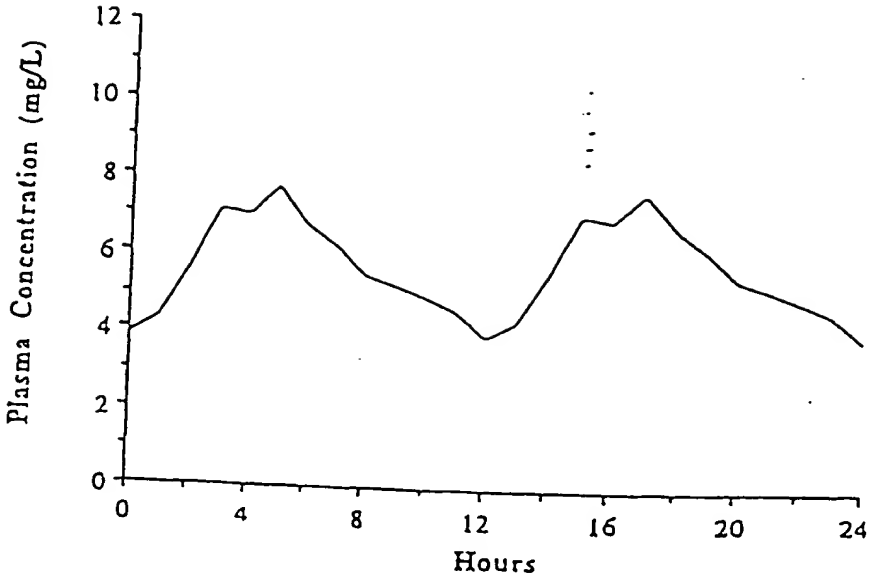

Figure 3

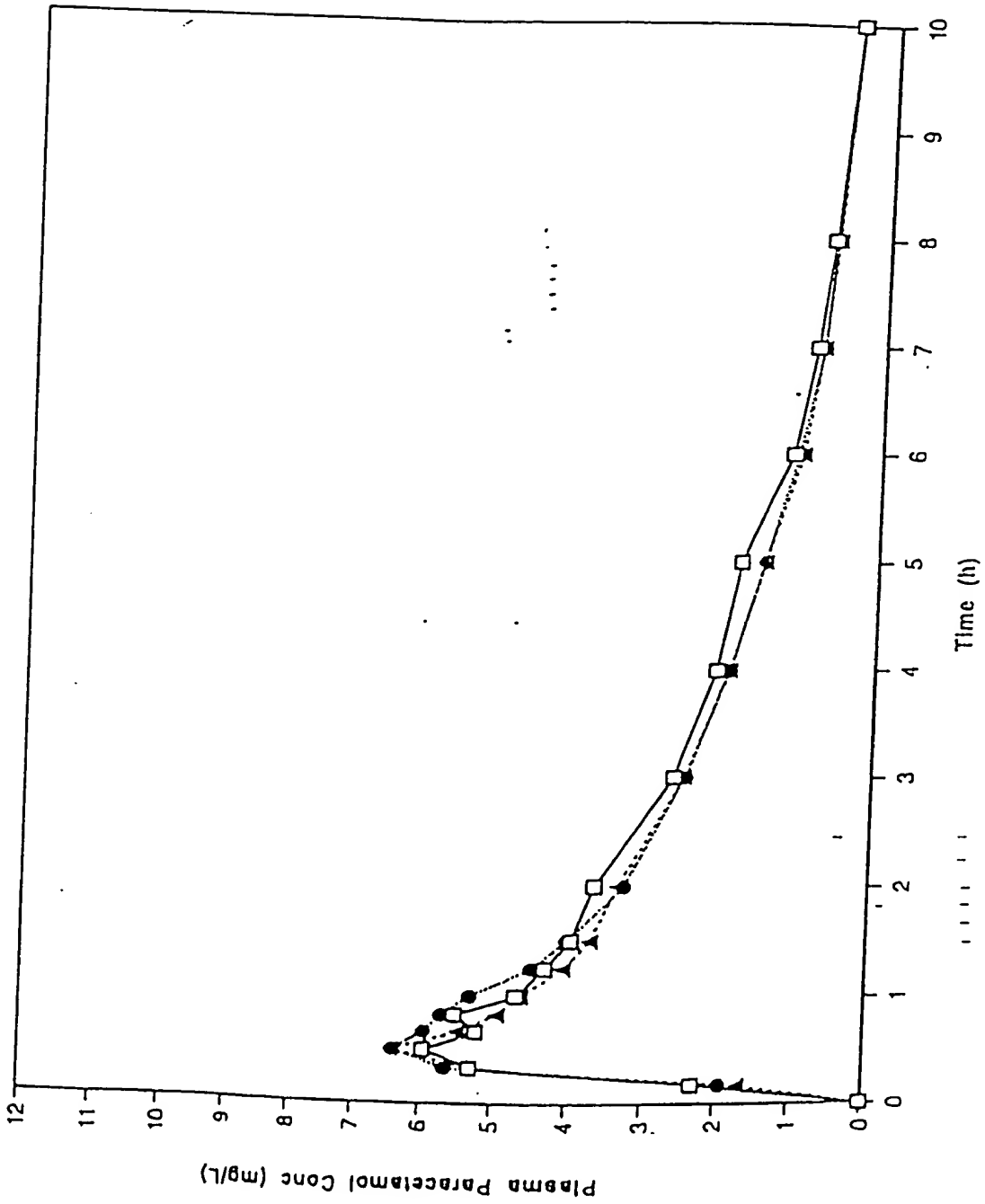
Plasma Paracetamol Conc (mg/L)
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (h)
0
1
2
3
4
5
6
7
8
9
10

Figure 4